Review article

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Tocolytic therapy in obstetrics

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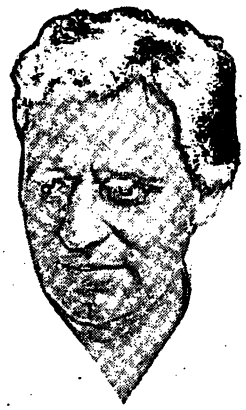
Tocolysis means drug-induced inhibition of premature or excessive uterine activity [38]. Other terms, such as "sedation of the irritated myometrium" or "relaxation of the uterus" have the same meaning; they are, however, not commonly applied [10, 11, 17, 29].

At the beginning of the research for new substances with inhibitory effect on the uterus it was postulated that progesterone or newly-developed **gestagen preparations could inhibit uterine activity.** In vitro as well as in vivo experiments showed that progesterone, in concentrations present during pregnancy [37, 56], exerts a synergistic effect on oxytocin and increases uterine activity. High concentrations which should be applied exclusively for experimental purposes showed the block inaugurated by Csapo [18]. Together with estrogen, progesterone increases the metabolic activity of the uterus. Prolonged influence leads to relaxation of the tissue and increased uterine weight. The collagen content as well as that of nucleic acids, glycogen, and lipids is raised. The sensitivity to exogenous irritation, e. g. uterine distension by the growing fetus, or to drugs, e. g. oxytocin, increases. Due to the low solubility in water, the considerable affinity to serum protein, and a half-life of 15 minutes, even the highest possible concentrations of progesterone cannot be expected to exert a sufficient effect on the myometrium [31, 36, 54].

Curriculum vitae



Karl Heinz Mosler *was born in Beuthen, Silesia, on November 5, 1927.*
1954 qualification as a physician at the University of Mainz.
1954—1956 hospital appointments in surgery and medicine.
1956—1960 appointment under Prof. Dr. Kuschinsky *at the Pharmacological Institute of the University of Mainz.*
1960 qualification as a pharmacologist.
From 1960 be worked at the Department of Obstetrics and Gynecology of the University of Würzburg under Prof. Dr. Schwalm. *In 1961 he started investigations on tocolysis. 1963 electronic equipment for intensive care and tocography was installed. In 1965 he qualified as an Obstetrican and Gynecologist and habilitated with "Dynamics of Uterine Muscle".*
1966—1967 Associate Professor at Washington University, St. Louis.
1968 University lecturer and Head-Physician at the Department of Obstetrics and Gynecology of the University of Würzburg.
1969 Chief of Department at the Department of Obstetrics and Gynecology of the University of Würzburg, where he established a laboratory for experimental and clinical Pharmacology of Gynecology and Obsterics and had started to develop an ultrasonic monitoring system since 1966.
1971 Professor of Gynecology and Obstetrics.
Fields of interests: Physiology and Pharmacology of uterine activity, labor irregularities, fetal ultrasonic cardiography, ultrasonic diagnostic, intensive supervision of mother and child during pregnancy and labor, prevention of premature labor, tocolysis.

1. Pharmacology of tocolysis

Cinnamedrine was the first β-adrenergic substance which, as reported by Schultz in 1940, showed a relaxant effect on the smooth muscle; however, it soon fell into disuse. In 1960 Lish et al. [35] published their findings concerning the relaxant effect on the isolated uterus of the β-adrenergic substance isoxsuprine. First clinical experiences with isoxsuprine were reported by

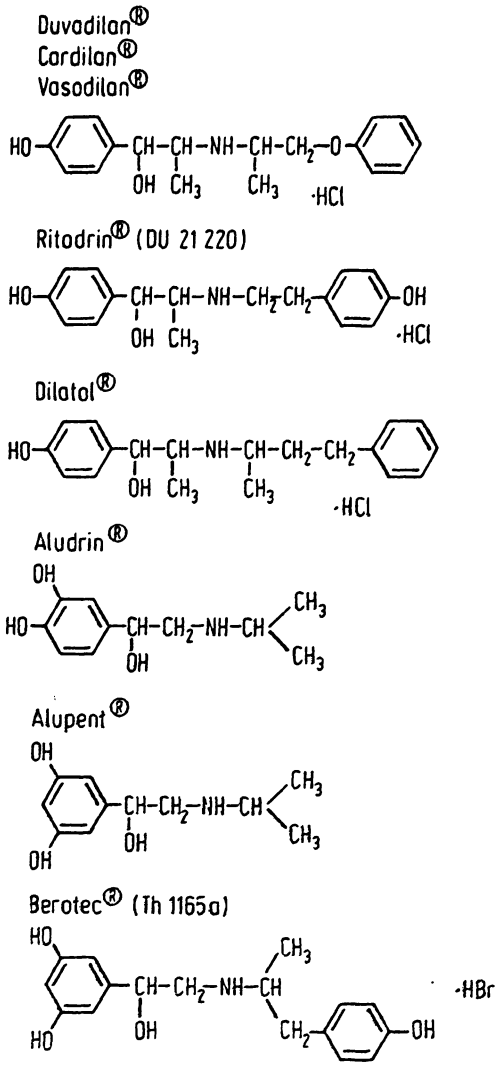


Fig. 1. Tocolytics, β-adrenergic stimulators.

HENDRICKS et al. [27] and BISHOP et al. [13] in 1960. These publications escaped notice in the German-speaking countries for some time. In 1961 we introduced nylidrin (buphenine, Dilatol®), a substance of similar composition which had already been tested on humans in Germany [17, 38, 55] (Fig. 1), into the treatment of premature labor.

Doses which were effective in the uterus led to considerable side effects. In subsequent years new β-sympathomimetics, last fenoterol (Th 1165a), were studied experimentally and therapeutically [17, 29, 38, 40]. Substances with a different mode of action, such as ethyl alcohol [24], spasmolytic agents of the calcium antagonistic type [23, 40, 41] and, recently, prostaglandin antagonists were also therapeutically tested [2, 43].

To date no drug which acts exlusively or primarily on the myometrium has been found.

1.1 β-Adrenergics

Tocolytics as such are substances with β-adrenergic effect on the myometrium. Among all the substances tested for their effectiveness in the inhibition of labor, the **β-adrenergics show the best effect with the lowest rate of side effects.** The effect on the uterus represents only one component in the total complex of reactions to adrenergic irritation. As to the various components of this spectrum, the catecholamines and their derivatives do not show a uniform activity. Two main groups of effects can be characterized. One can be easily induced by norepinephrine but not at all or only slightly by use of isoproterenol. The second group is easily induced by isoproterenol, but in most cases not by norepinephrine. In view of this phenomenon, AHLQUIST [1] postulated **two types of adrenergic receptors, α and β,** and two types of adrenergic drugs, α-adrenergic substances (prototype: noradrenalin) and β-adrenergic substances (prototype: isoproterenol). At present the following pattern of action can be described:

α-receptors: General excitation of the smooth muscles, in particular of the vessels; activation of hepatic glycogenolysis.

β_1-receptors: Positive inotropic, chronotropic and bathmotropic effects on the heart, relaxation of the intestinal muscles, stimulation of lipolysis.

β_2-receptors: Likewise lytic effects on the intestinal muscles as well as on the smooth muscles of bronchi, muscular arterioles and uterus; activation of the muscular glycogenolysis.

DAVIS et al. [20] regard the receptors as isoenzymes. According to the pattern of the isoenzyme the effect of the agonists of one substance group varies between different individuals and different tissues. At present the **β-receptor is regarded as an integrating component of the adenyl cyclase system, the β-adrenergic effect being based upon an increase of the intracellular cAMP level.** It is still not completely clear in which way cAMP leads to the relaxation of the muscle cell and to glycogenolysis, lipolysis and

protein synthesis in the cell [52]. SCHILD [46] and RASMUSSEN et al. [45] postulated calcium as the main factor for the contracting and relaxant effect of sympathomimetics. According to ANDERSON et al. [3] the effect of the β-receptor stimulation is reflected by an increased formation of cAMP; they assume a stimulation of the calcium accumulation in the microsomal fraction of the smooth muscle. The effect on the muscular tone as well as on the cAMP level can be prevented by β-blockers [4, 5, 6].

In search of new β-adrenergic substances with **better tolerance and increased effectiveness,** isoxsuprine (Duvadilan®), nylidrin (Dilatol®) and other derivatives, such as Ritodrine®, orciprenaline (Alupent®) and the trial drug Th 1165a fenoterol (Partusisten®) were used experimentally and clinically for the inhibition of labor [14, 15, 21, 22].

JUNG confirmed that among the tocolytics tested, fenoterol, Th 1165a (Partusisten®) shows the best results with the lowest dosage. Since 1968 we have applied Th 1165a routinely in the treatment of premature labor. Using intravenous drip infusion an immediate tocolytic effect is obtained which can easily be controlled. In selected cases oral administration of Th 1165a, too, leads to remarkable inhibition of labor; this effect is obtained within 20 minutes. The following side-effects were observed in 5% of the patients: Restlessness, muscle tremor, sensations of warmth and heat, flushing of the face, nausea. An increased pulse rate occurs in mother and child. When intravenous infusion therapy is used, these symptoms are generally found only at a dosage of more than 2 μg/min. For the evaluation of possible side effects on the fetus, the whole spectrum of β-stimulating changes has to be considered; i. e. in addition to positive inotropic and chronotropic effect and vasodilation in particular metabolic changes such as glycogenolysis and lipolysis must be mentioned [48]. **Serious sequelae of these side-effects have not been reported** [42].

1.2 Spasmolytics of the papaverine type

Those women treated with Dilatol® in our hospital since 1963 complained above all of an **uncomfortable increase in heart-rate.** Therefore

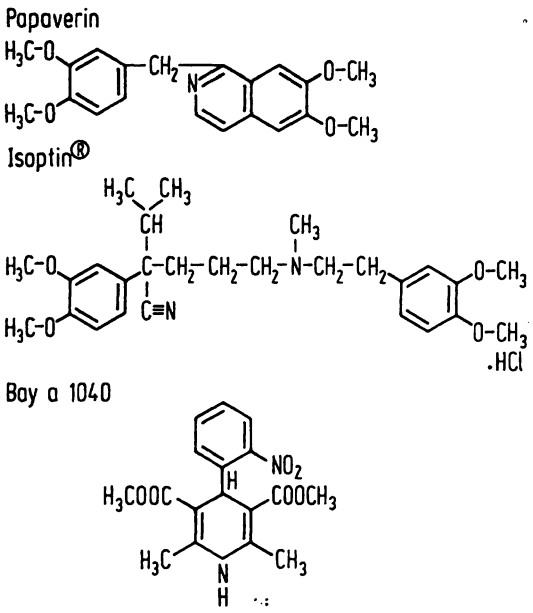


Fig. 2. Spasmolytics.

the β-adrenergic substance was then combined with papaverine (Fig. 2). The combination of these two compounds with their different modes of action was meant to increase the inhibitory effect on the uterus, at the same time reducing the side-effects described above.

In 1914 PAL [44] discovered the **relaxant effect of papaverine on the smooth muscle.** In the human uterus high doses lead to reduced tone and decreased frequency of uterine contractions; inhibition, however, is only obtained with the highest possible concentrations. Paperverine has a negative inotropic effect on the cardiac muscle and reduces blood pressure by peripheral vasodilation. These and other side-effects elicited by the high concentrations required, made the cli-

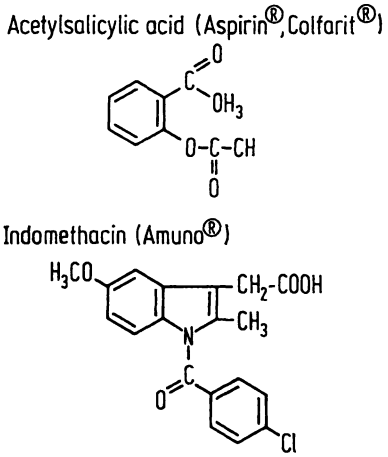


Fig. 3. Antipyretics.

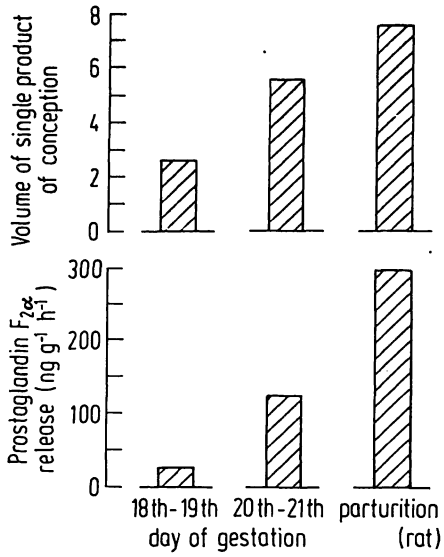


Fig. 4. Growth of the fetus and prostaglandin release in the pregnant rat (according to AIKEN) during the last 5 days before delivery.

nical implementation of such uterine inhibition impossible.

HAAS and HÄRTFELDER [25] developed verapamil (Isoptin®). Both substances — papaverine as well as verapamil — exert a spasmolytic-musculotropic effect and are regarded as calcium antagonists. According to FLECKENSTEIN [23], electromechanic decoupling leads to inhibition of the calcium influx through the depolarized membrane. From in vivo as well as in vitro experiments it became evident that **verapamil has an inhibitory effect on the uterus** 5 times as strong as papaverine. Even with an acceptable dosage, however, its effect is inferior to that of Th 1165a. **Tachycardia following Th 1165a, which some patients regarded as particularly unpleasant was reduced by simultaneous administration of verapamil.** As is shown in the studies conducted by WEIDINGER and WIST

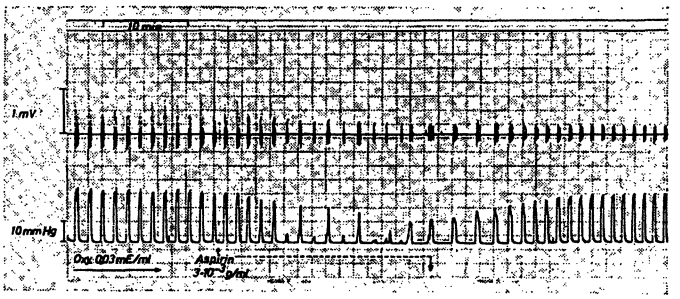


Fig. 5. Mechanic and electric activity of the isolated rat uterus following stimulation by oxytocin. In high concentrations aspirin exerts a direct inhibitory effect on the uterine activity.

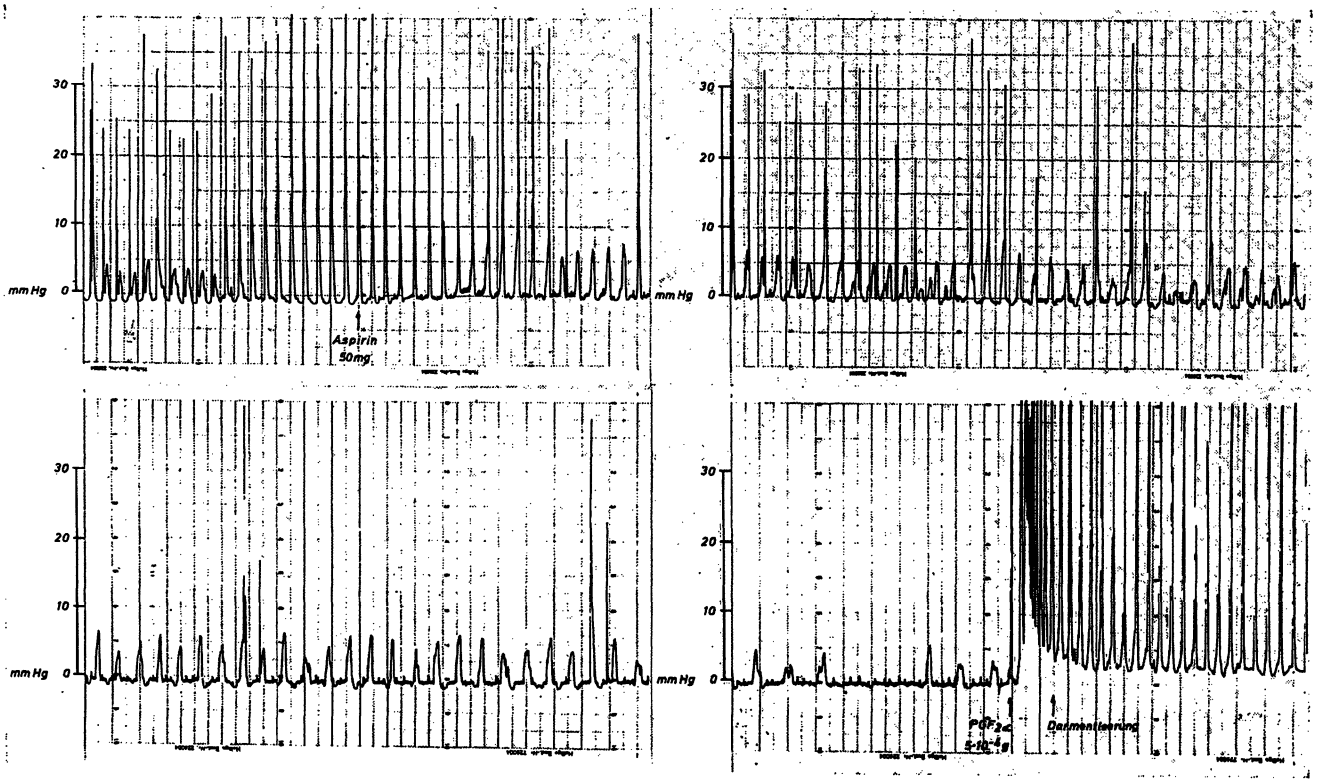
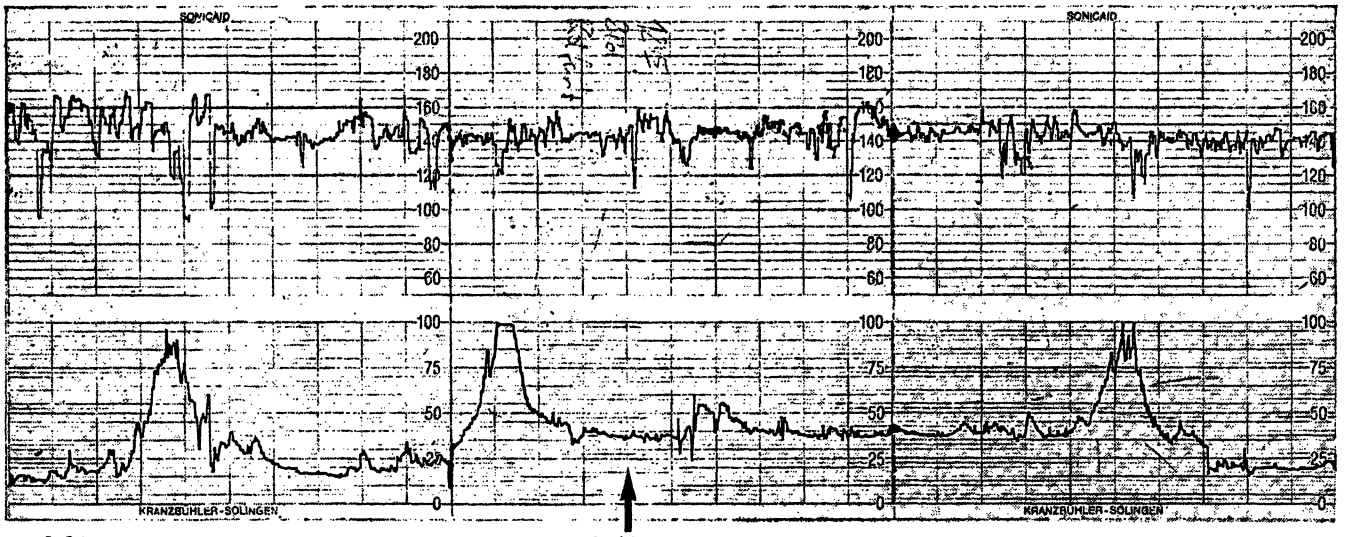
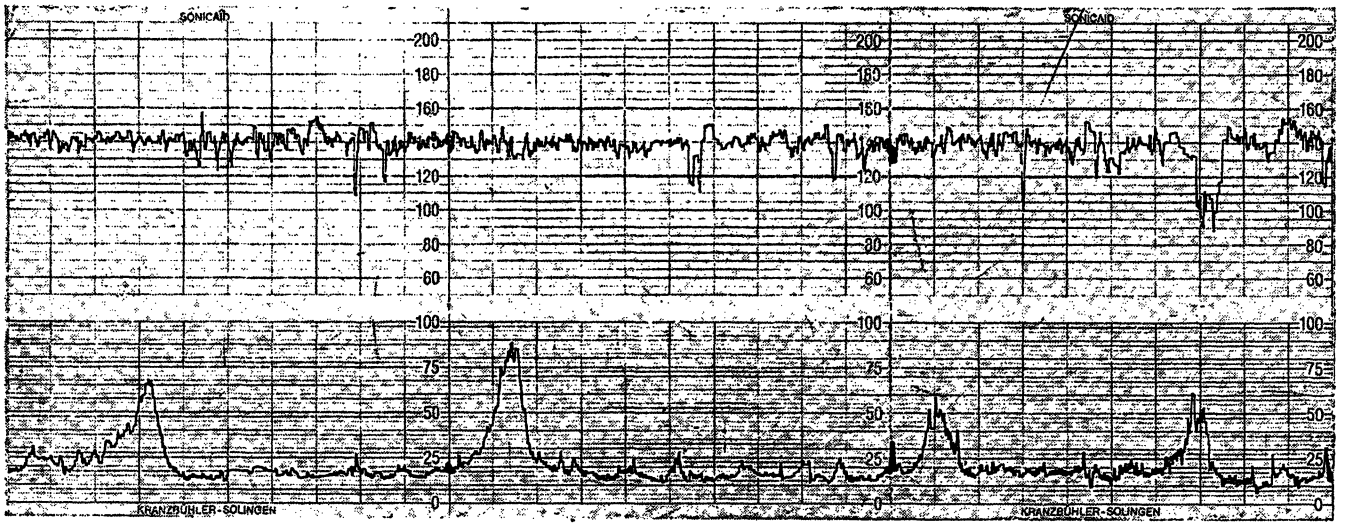


Fig. 6. In the anesthetized rat Aspirin® inhibits the oxytocin-induced uterine activity (rectal application). Intravenous application of prostaglandin $F_{2\alpha}$ leads to renewed uterine activity.





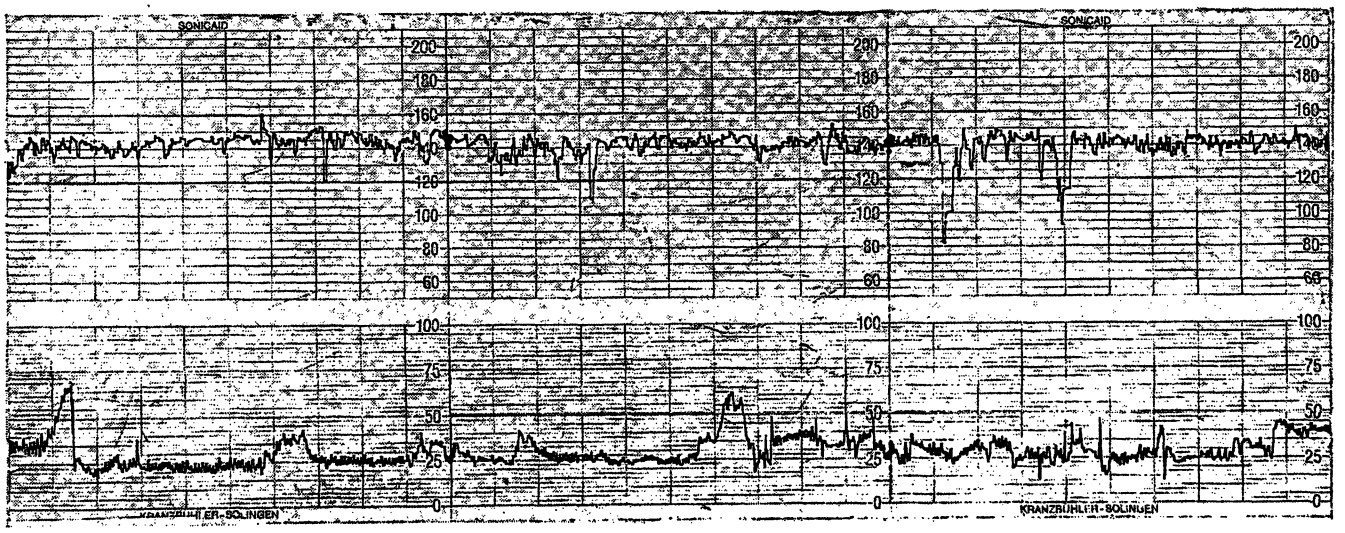


Fig. 7. Ultrasonic cardiotocography in human. Colfarit® (Aspirin®) 1 g orally, reduces the uterine activity in the case of premature labor. Slow onset and effect lasting several hours has been observed.

[53] the **metabolic side-effects of the β-sympathomimetics are also decreased by verapamil. Prostaglandins** are involved in the process of uterine contractility [30]. **Anti-inflammatory or antipyretic agents** of the Aspirin® or indomethacin type (Fig. 3) **reduce uterine activity by inhibition of prostaglandin formation and release.** VANE [50] demonstrated in animal experiments that prostaglandinsynthesis and release can be diminished by Aspirin® or indomethacin. AIKEN found an increase in PGE and PGF like prostaglandins depending upon the length of gestation. Rat uteri during parturition produced 20 times more PGF-like substances than uteri at 18—19 days of gestation (Fig. 4). The distension of the uterine wall by the growing fetus stimulates the process of prostaglandin formation.

Animal in vitro and in vivo experiments (Figs. 5 to 6) led us to evaluate the effect of long-term use of Aspirin® in the treatment of threatened premature labor. In clinical trials we were successful in inhibiting premature uterine contractions with Aspirin® (Fig. 7). In the demonstrated case at thrity-eight weeks gestation, Aspirin® was discontinued and spontaneous labor ensued in 4—8 days.

A retrospective survey has been carried out with 103 patients [F. FUCHS, personal communication]. FUCHS had taken high doses of acetylsalicylic acid for at least the last 6 months of pregnancy and a comparative study with a suitable population has been made. Use of Aspirin® was associated with a marked and highly significant increase in the average length of gestation, in the incidence of postmaturity, and in the mean duration of spontaneous labor.

The possible acting mechanism of Aspirin® is shown in Fig. 8.

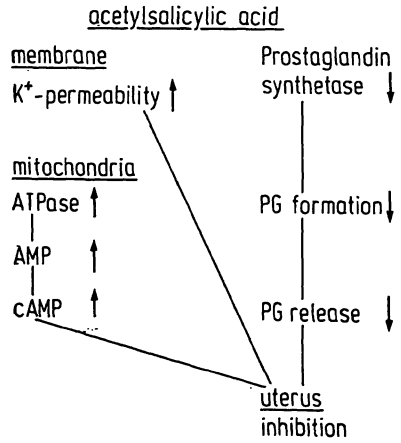


Fig. 8. Mechanism of direct action of aspirin on the uterus.

1.3 Ethyl alcohol

Ethyl alcohol is recommended for the inhibition of labor by F. FUCHS [24]. He attributes the **labor-inhibiting effect to blocked oxytocin release in the neurohypophysis.** J. HÜTER [28] could confirm known labor-inhibiting and basal tone decreasing properties of ethanol in the isolated uterus of rats and mice; ethyl ether and halothane are also known to possess these properties. Therefore a peripheral point of attack cannot be excluded.

With the dosage indicated by F. FUCHS, the blood alcohol level ranges from 0.10 to 0.16%. In addition, adequate intake of hard liquor tenders oral treatment possible.

1.4 Other substances with inhibitory effect on the uterus

Progesterone, gestagen, opiates, and benzodiazepine are only of historical interest, since an inhibitory effect could not be proved in clinical tests. Relaxin, atropine, antihistamine, and phenothiazine have also been given without success for the inhibition of labor [51].

Among the **opiates** there are likewise no substances which, in a therapeutically acceptable dosage, could sedate the uterus. These substances may prove detrimental in case of fetal asphyxia and may lead to hypoventilation, especially in the premature fetus. Librium® and Valium® are no labor-inhibiting agents. Their spasmolytic effect is similar to that of papaverine. With therapeutical dosage intrauterine tocometry did not show any labor-inhibiting effect in humans [7, 8, 9]. In some cases we use benzodiazepine for psychical sedation as well. If required, analgetics should also be given.

Theophylline is not being used for tocolysis since we have the more effective β-adrenergic substances and spasmolytics. It was recently shown that the effect of theophylline on the nonpregnant human uterus is that of relaxation, independent of the phase of the cycle [16, 19].

Due to toxicity or marked side effects, some substances with tocolytic properties cannot be used as a routine measure. Intravenous application of magnesium sulfate leads to pronounced reduction in contraction frequency and amplitude. However, the required blood level concentration of 8 to 12 mg% is very close to the toxic threshold dose [51].

Among the **inhalation anesthetics,** ether and chloroform are known to exert an especially strong effect on the uterus.

Chloroform is no longer used because of its narrow therapeutic range and the danger of organic lesions. Although ether shows an excellent relaxant effect it cannot be recommended mainly because of the fact that it may lead to vomiting with danger of aspiration and hypoxia of the fetus [28].

The pharmacological and anesthesiological properties of **halothane** are of value for obstetrics: non-inflammability, rapid onset and subsiding of anesthesia without excitation, and rapid tocolysis. If general anesthesia is required, e. g. in case of prolapse of the cord, halothane is the appropriate anesthetic. The following disadvantages are to be mentioned: occasional cardiac irregularities and hypoventilation, insufficient relaxation of the striated muscles, passage into the fetal circulation with danger of hypoxia [28]. Halothane sensitizes the heart to catecholamines. Cases of oxytocin-resistant uterine atony have been reported [51].

2. Clinical conditions required for tocolysis

Modern tocolytics are highly effective drugs. Therefore, tocolysis must be restricted to hospitals staffed with obstetricians. **Continuous monitoring and personal observation during treatment** should be possible. The development of efficient instruments in the last few years for the external control of fetal cardiac activity and uterine activity (phonocardio-tocograph (CTG) developed by HAMMACHER [26], ultrasonic-cardio-tocograph (USCTG) developed by MOSLER [39]) may be regarded as advantageous to large-scale clinical application of drugs for the inhibition of labor.

In particular the diagnosis "increased uterine activity" should be confirmed clinically using tocography. Biliary as well as ureteric and intestinal spasms are sometimes mistaken for premature labor.

In latter years the number of indications for tocolysis has increased. This supplemented indication list enables a more exact and therefore more successful determination for tocolysis. A reduction in the number of premature deliveries may give rise to hopes of a decrease in perinatal mortality [8, 10, 11, 18, 29, 43]. Initial reports on favorable results obtained with tocolysis are tempered with more pessimistic evaluations [34, 42, 58].

Successful tocolysis requires certain conditions.

2.1 Clinical requirements for tocolysis

a) Coordinate labor with a frequency of **1 or more contractions within 10 minutes** (tocography, partogram).
Contractions can often be reduced, by moving the patient into a **lateral position.** Patients statements regarding pain during contractions are no reliable criterion for their intensity [28].

b) The parturient patient must be carrying a **live fetus.**

c) Estimated **fetal weight below 2500 g,** or gestation period up to the 37th week.

d) The **cervix is dilated not more than 3 cm.**

e) The **cervix is effaced no more than 50%** (pelvic score).

2.2 Relative clinical contraindications

a) Obstetric contraindications
Premature rupture of the membranes of the lower pole,
Temperature above 38°C in case of suspected intrauterine infection,
Severe hemorrhage in case of placenta praevia,
Premature separation of the placenta,
Cephalo-pelvic-disproportion, and contracted pelvis.

b) Medical contraindications with respect to the fetus
Pathological pattern of the heart rate,
Confirmed malformations,
Erythroblastosis,
Polyhydramnios.

c) Medical contraindications with respect to the mother
Diabetes mellitus which is difficult to stabilize,
Hyperthyroidism,
Congenital heart disease; heart lesions, e. g. fibrillation.
Owing to the danger of sudden cardiac death, catecholamines should be used very cautiously in cases with coronary sclerosis, hyperthyroidism, and severe hypertension. Concurrent administration of calcium ions increases the tendency to ventricular fibrillation [33].

In the present article pharmacological contraindications are mentioned only briefly. A detailed description is given in a separate publication on the side-effects of β-adrenergic tocolytics. Drug-induced inhibition of premature labor must be preceded by a general medical examination, including auscultation of the heart in particular.

There is almost complete agreement on the clinical conditions required for tocolysis; however, as to the parameters which are considered relative contraindications widely differing opinions have been published. BIENARZ, CIBILS, FUCHS, and LANDESMAN [59] regard premature rupture of the membranes as a contraindication because of the danger of ascending infection. On the other hand, KOEPCKE and SEIDENSCHNUR [32] as well as WEIDINGER and WIEST [53] report on successful inhibition of labor following premature rupture. Without tocolysis rupture leads to spontaneous delivery within 3 days in 60% of all cases. In 8% of all cases, the pregnancy is maintained until the end of the gestation period. In the individual case tocolysis may be tried in case of rupture. A prolongation of the gestation period by more than 8 days should be achieved, this to be weighed against the danger of infection for mother and child. According to our own experience, we regard rupture with considerable loss of amniotic fluid as a contraindication for tocolysis.

3. Indications for tocolysis

The main field of application for tocolytics is **in threatened premature labor.** Premature delivery plays an important part in perinatal mortality [8, 55]. Countries with a low number of premature deliveries have better statistics concerning perinatal mortality, e. g. Sweden as compared to the USA. Before a treatment is begun, however, we have to ask ourselves if it is advantageous to prevent premature delivery in every case. ZSUSPAN points to the increasing number of children with disturbances of the central nervous system; he finds it difficult to determine to what extent these disturbances can be attributed to prematurity [59].

In our opinion, **prophylactic long-term medication** is not indicated. "Prophylactic therapy", in case of recurrent premature labor, must be restricted to clinical observation or to regular supervision in the outpatient clinic. Additional measures must be taken to solve the problem of premature delivery:

1. Family planning,
2. Adequate prenatal care,
3. Better social condition of the pregnant woman
4. Inhibition of premature labor as early as possible using specific drugs.

On the other hand we approve of **prophylactic use of tocolytics in the short-term medication,** e. g. after surgical treatment of the uterus in pregnancy. In addition, short-term tocolysis will generally be given to bridge the time until delivery in cases of fetal distress. In case of administration of β-adrenergic substances for several hours after surgical operations, the development of intestinal atony must be considered. Therefore we use post-operative tocolysis according to the contraction pattern registered by a monitor.

The indications for tocolysis listed below will subsequently be briefly commented:

A. **Premature labor with excessive uterine activity**

We do not start tocolysis before the 28th week of gestation because the β-stimulators have only a weak effect in early pregnancy. JUNG et al. [29] obtained favourable results in the treatment of imminent abortion with a drip infusion during the 2nd to 4th month of pregnancy.

B. **Regulation of labor sub partu**

a) In cases with hyperactivity and hyperkinesis (e. g. precipitate labor in case of transverse lie, imminent uterine rupture)

b) In some forms of hypertensive dystocia and uncoordinated uterine contraction (increased basal tone, uterine tetanus)

c) As an antidote in uterine hyperstimulation due to oxytocin or prostaglandin (oxytocin sensivity test, induction of labor).

With strong frequent contractions only incomplete transitory inhibition can be obtained [38]. Complete inhibition cannot be achieved with

β-sympathomimetics. We have been able to observe, (as have KOEPCKE and SEIDENSCHNUR [32]), that after discontinuance of the tocolytic therapy an extremely rapid dilation of the cervix may occur.

C. **Surgical treatment during pregnancy on the uterus:**
Cerclage according to SHIRODKAR or MC DONALD,
Myoma enucleation,
Hysterotomy,
Intrafetal transfusion in erythroblastosis.
Other operations:
e. g. appendectomy
surgical treatment of biliary or renal stones.

D. **Obstetric emergency cases**
Complications involving the umbilical cord,
Versions and extractions,
Manual removal of the placenta.

E. **Mild to medium hemorrhage due to placenta praevia** up to the 37th week of gestation
The decision whether to apply conservative methods in case of placenta praevia bleeding depends on the individual clinical situation. Even with severe bleeding the uterus may be sedated to prevent further separation of the placenta until delivery or caesarean section.

F. **Intrauterine asphyxia in the course of labor** (so-called "intrauterine reanimation" until delivery)
As a symptom for fetal hypoxia, marked deceleration of the child's heart-rate may occur during delivery. CALDEYRO-BARCIA et al. [15] as well as MOSLER [40] demonstrated successful intrauterine treatment of the fetus in fetal distress by means of administration of orciprenaline or fenoterol (Th 1165a), respectively, to the mother. In the meantime appropriate measures for completion of parturition may be taken. In some cases delivery can be spontaneous. The blood gas analysis showed an increase of the pH-value under tocolysis [15].[1]

G. **Gestosis** (reduction in blood-pressure, simultaneous stimulation of the utero-placental blood-flow, additional infusion of a plasma expander).
VAHRSON and SCHWARZ [49] assume an increased utero-placental blood flow, in view of the marked reduction of blood pressure in the mother without danger for the child. ZAPIOLA [57] reported on angiographical studies in pregnant women with increased risk: β-stimulation increases human utero-placental circulation. This therapy, designed to improve the placental ischemia, is problematical in cases already demonstrating alterations of the placenta.

4. Management of threatened premature labor

We have adopted the following scheme in our clinical management of threatened premature labor

A. **Bedrest and mild sedation:**
For cases in which continuous uterine monitoring has demonstrated only irregular premature uterine contractions (prematurity in past medical history).

B. **Combined tocolytic-spasmolytic administration:**
For cases in which continuous uterine monitoring has demonstrated regular uterine contractions (prematurity in past medical history).

Immediate treatment — intravenous
Th 1165a 1—3 μg/min
Verapamil 120 μg/min
(administered in 500 ml 5% Glucose).

Long-term treatment — oral
Th 1165a 3 mg every 4—6 hours
Verapamil 40 mg every 4—6 hours.

If there is no sufficient inhibition of labor, Aspirin® is given in addition
1 g every 6 hours for 2—6 days orally or rectally.

Keywords: Alcohol, Aspirin®, β-adrenergics, halothane, premature labor, tocolysis, uterus.

Zusammenfassung

Tokolytische Therapie in der Geburtshilfe

Unter Tokolyse versteht man die medikamentöse Hemmung vorzeitiger oder überschießender Uterusaktivität. Progesteron oder inzwischen neuentwickelte Gestagen-Präparate können die Uterusaktivität des Menschen nicht überzeugend hemmen. Progesteron-Konzentrationen, die in der Schwangerschaft vorkommen, können sogar synergistisch zum Oxytocin wirken und die Uterusaktivität steigern. Nur die im Experiment anwendbaren hohen Konzentrationen zeigen den von CSAPO inaugurierten Block. Bewiesen wurde, daß Progesteron zusammen mit Östrogen die Stoffwechselaktivität des Uterus erhöht, es steigert den Kollagen- sowie den Nucleinsäure-, Glykogen- und Lipidgehalt. Therapeutisch angewendet kann es wegen seiner geringen Wasserlöslichkeit, der hohen Affinität zum Serumprotein und der kurzen Halbwertzeit auch in höchstmöglichen Konzentrationen keinen ausreichenden Effekt erzielen.

1. Pharmakologie der Tokolyse

Die **β-adrenergen Substanzen (Fig. 1),** kontinuierlich in kleinen Konzentrationen zugeführt, haben einen guten tokolytischen Effekt. Über erste klinische Erfahrungen berichteten HENDRICKS und Mitarb. sowie BISHOP und Mitarb. Nylidrin (Buphenin, Dilatol®) fand bei uns Eingang in die Therapie vorzeitiger Wehen. Ridotrin® und Partusisten® zeigten von den später untersuchten Substanzen die beste Wirkung bei geringer Nebenwirkung.
β-Blocker heben die Wirkung der β-Stimulatoren auf. **Spasmolytika vom Papaverintyp (Fig. 2) können ähnlich wie β-Blocker die Herzwirkung der β-Stimulatoren reduzieren, gleichzeitig aber am Uterus synergistisch zum β-Stimulator wirken.** Verapamil (Isoptin®) hat einen spasmolytischen, muskulotropen Effekt und schien für eine Kombination mit β-Stimulatoren geeignet. Verapamil hat eine 5mal stärkere uterushemmende Wirkung als Papaverin, kann aber bei geringer Nebenwirkung höher dosiert werden.
Die **nichtsteroiden, entzündungshemmenden Stoffe (Fig. 3)** können bei längerer Einwirkung die Uterusaktivität hemmen, sie gelten als **Prostaglandinantagonisten (Fig. 4—6).** Prostaglandine der Fraktion E_2 und $F_2\alpha$ gelten als Mediatoren der Uterusaktivität. Die Hemmung ihrer Synthese könnte als kausale Therapie bezeichnet werden, wenn man voraussetzt, daß natürliche Prostaglandine zur vorzeitigen oder überschießenden Uterusaktivität führen. In einigen Fällen konnte im klinischen Einsatz **Acetylsalicylsäure** in Form von Colfarit® oral oder als Aspirin®-Supp. gegeben werden **(Fig. 7—8).** Die Dosis betrug bis maximal 6 g täglich. Wegen der zu erwartenden Nebenwirkungen des Aspirins®, z. B. auf das Gerinnungssystem und einer möglichen Kumulation, wurde die Therapie fraktioniert, d. h. nach 6 Tagen unterbrochen, und bei erneutem Einsetzen von Wehen wieder begonnen.

Äthylalkohol kann in Konzentrationen von 1,0—1,6‰ die Uterusaktivität reduzieren.

Magnesiumsulfat führt zu einer Verminderung der Wehenfrequenz und -Amplitude. Die erforderliche Blutspiegelkonzentration liegt jedoch mit 8—12 mg% sehr nahe an der toxischen Grenze.
Äther zeigt am Uterus eine hervorragende relaxierende Wirkung, kann aber wegen des postnarkotischen Erbrechens mit Aspirationsgefahr nicht generell empfohlen werden.
Die anästhesiologischen Eigenschaften von **Halothan** sind für die Geburtshilfe günstig, da es zu einer schnellen Tokolyse führt. Als Nachteile gelten Herzirregularitäten und Atemdepressionen mit Übergang in den fetalen Kreislauf und der Gefahr der Atemdepression.

2. Klinik der Tokolyse

Die modernen Tokolytika sind hochwirksame Pharmaka, deshalb sollte die Tokolyse Kliniken mit ärztlicher Geburtshilfe vorbehalten bleiben. Eine **apparative und personelle Dauerüberwachung** während der Behandlung sollte möglich sein. Für die externe Dauerüberwachung eignen sich der Phonokardiotokograph und der Ultraschallkardiotokograph.
Die größte Hoffnung auf eine Verringerung der perinatalen Mortalität könnte durch die Senkung der Frühgeburtenzahl erzielt werden. Für eine erfolgreiche Tokolyse sind einige Voraussetzungen erforderlich:

1. **Koordinierte Wehentätigkeit** mit einer Frequenz von 1 und mehr Wehen in 10 Minuten.
2. **Lebender Fet.**
3. Geschätztes **Gewicht des Feten unter 2.500 g** bzw. Tragzeit bis zur 37. Woche.
4. **Muttermund bis maximal 3 cm** eröffnet.
5. **Zervix weniger als die Hälfte verkürzt.**

Als **relative klinische Kontraindikation** gelten: der vorzeitige Blasensprung, Temperaturen über 38°C bei Verdacht auf intrauterine Infektion, starke Blutungen bei Placenta praevia, vorzeitige Plazentalösung sowie Mißverhältnis, z. B. bei engem Becken.
Als **relative medizinische Kontraindikation von seiten des Feten** gelten: pathologische Herzfrequenzmuster ohne Wehen, nachgewiesene Mißbildung, Erythroblastose und Hydramnion mit Verdacht auf Mißbildung.
Als **relative medizinische Kontraindikation von seiten der Mutter** haben zu gelten: ein manifester schwer einstellbarer Diabetes mellitus, angeborene Herzkrankheiten, kardiale Arrhythmien, Hyperthyreose und schwere Hypertonie. Gleichzeitige Gabe von Kalziumionen verstärkt die Tendenz zum Kammerflimmern.

3. Indikation zur Tokolyse

1. **Vorzeitige Wehentätigkeit** mit drohender Frühgeburt.
2. **Wehenregulierung** bei Hyperaktivität des Uterus, Tetanus uteri,

Antidot bei Überstimulierung mit Oxytocin oder Prostaglandinen.

3. **Operationen** in graviditate
   Cerclage
   Myomenucleation
   intrafetale Transfusion bei Erythroblastose
   andere abdominale Operationen.

4. **Geburtshilfliche Notfälle**
   Nabelschnurvorfall,
   Wendung und Extraktion
   Manuelle Plazentalösung
   Involutio uteri post partum, Reposition

5. Schwache bis mittelstarke **Placenta-praevia-Blutung** bis zur 37. Gestationswoche.

6. **Intrauterine Asphyxie** in der Austreibungsperiode.

7. **Gestose.**

4. Behandlung der drohenden Frühgeburt

Nach folgenden Richtlinien kann die klinische Behandlung der drohenden Frühgeburt durchgeführt werden:

a) Bettruhe und leichte Sedierung in Fällen von unregelmäßiger vorzeitiger Uterusaktivität.

b) Kombinierte tokolytische und spasmolytische Therapie in Fällen, in welchen die kontinuierliche Uterusaktivität in stärker werdende, reguläre Uterusaktivität übergeht.

Die **akute Behandlung** beginnt intravenös mit β-Stimulatoren, z. B. Th 1165a 1—3 μg/min, zur Vermeidung von Nebenwirkungen Verapamil 120 μg/min in 5%iger Glucoselösung.

Langzeitbehandlung oral Th 1165a 3—5 mg alle 4—6 Stunden, Verapamil zusätzlich 40—80 mg alle 4—8 Stunden.

Setzt keine ausreichende Hemmung der Wehentätigkeit ein, dann kann der Versuch unternommen werden, Aspirin 1 g alle 6 Stunden für 2 maximal 6 Tage oral oder rectal zuzuführen.

Schlüsselwörter: Äthylalkohol, Aspirin, β-Adrenergika, Halothan, Wehen (vorzeitig), Tokolyse.

Résumé

Thérapie tocolytique en obstétrique

Par tocolyse on entend l'inhibition médicamenteuse de l'activité utérine prématurée ou excessive. Le progestérone ou les préparations de gestagènes mises au point entretemps ne peuvent pas inhiber de façon convaincante l'activité utérine humaine. Les concentrations de progestérone qui se produisent dans la grossesse peuvent même avoir un effet synergétique d'oxytocine et accroître l'activité utérine. Seulemente les concentrations élevées applicables en expérimentation montrent le bloc inauguré par CSAPO. Il a été prouvé que le progestérone avec l'oestrogène augmente l'activité métabolique de l'utérus ainsi que la teneur en collagènes de même qu'en acide nucléique, glyogène et lipides. Appliqué de façon thérapeutique, il ne peut pas atteindre un effet suffisant même sous forme de concentrations maximales en raison de son hydrosolubilité réduite, de sa grande affinité avec la plasmaprotéine, et de sa courte période de demi-valeur.

1. Pharmacologie de la tocolyse

Les **substances β-adrenergiques (Fig. 1),** administrées de façon continue en concentrations faibles ont, un bon effet tocolytique. HENDRICKS et coll. ainsi que BISHOP et coll. ont parlés des premières expériences cliniques. La nylidrine (buphénine, dilatol®) etait employée chez nous en thérapie pour les douleurs prématurées. Parmi les substances examinées par la suite, la ridotrine® et les partosistes® se montrèrent les plus efficaces avec un effet secondaire réduit.

Les agents β bloqueurs stoppent l'effet des β stimulateurs. Des **substances spasmoly-figures (Fig. 2) du type de papavérine peuvent, de façon similaire aux β blockeurs, réduire l'effet cardiaque des β stimulateurs, mais agir en même temps de façon synergétique sur l'utérus comme un β stimulateur.** Le verapamil (isoptin®) a un effet spasmolytique, musculotrope et a semblé convenir à une combinaison avec les β stimulateurs. Le verapamil a un effet inhibiteur sur l'utérus 5 fois supérieur à celui de la papavérine et, en cas d'effet secondaire réduit, son dosage peut être encore augmenté.

Les **agents nonstéroides, inhibitrices des inxammations (Fig. 3),** peuvent, sous action prolongée, inhiber l'activité de l'utérus et ont valeur **des antagonistes des prostaglandines (Fig. 4—6).** Les prostaglandines de la fraction E_2 et $F_2\alpha$ sont considérées comme des médiateurs de l'activité utérine. L'inhibition de leur synthèse pourrait être qualifiée de thérapie causale si on part du fait que les prostaglandines naturelles conduisent à une activité utérine prématurée ou excessive. Dans quelques cas, on a pu, en intervention clinique, administrer de **l'acide acétyle salicylique** sous forme de colfarit® par voie buccale ou de suppositoires d'aspirine® **(Fig. 7—8).** La dose maximale a été de 6 g par jour. A cause des effets secondaires probables de l'aspirine, sur le système de coagulation par exemple, et d'une cumulation éventuelle, la thérapie a été fractionnée, c. à. d. interrompue après 6 jours pour être recommencée à la reprise des douleurs.

L'alcool éthylique, concentré à 1,0—1,6‰, peut réduire l'activité utérine.

Le sulfate de magnésium provoque une diminution de la fréquence et de l'amplitude des douleurs. Mais la concentration du taux sanguin requise étant de 8—12 mg%, elle se trouve très près de la limite toxique.

L'éther manifeste dans l'utérus une excellente action relaxante, mais ne peut malgré tout pas être recommandé d'une façon générale à cause des vomissements postnarcotiques avec risque d'aspiration.

Les propriétés anesthésiologiques de l'**halothan** sont favorables en obstétrique, car il provoque une tocolyse rapide. Les inconvénients en sont, toutefois, les irrégularités cardiaques et dépressions respiratoires avec passage dans la circulation foetale et danger de dépression respiratoire chez le nouveau-né.

2. Aspects cliniques de la tocolyse

Les tocolytica modernes sont des médicaments très efficaces; la tocolyse devrait donc être réservée aux hôpitaux dotés d'un service médical d'obstétrique, **avec surveillance assurée en permanence pendant le traitment par un personnel et des appareils suffisants.** Le phonocardiotocographe et l'ultrasonocardiotocographe sont recommandés pour la surveillance permanente externe.
On peut espérer réduire la mortalité périnatale en premier lieu en abaissant le nombre des accouchements prématurés. Une tocolyse réussie présuppose:

1. un travail **d'accouchement coordonné** avec une fréquence de 1 à plusieurs douleurs par dix minutes;
2. un **foetus vivant;**
3. un **poids du foetus estimé inférieur à 2500 g** ou une durée de grossesse n'ayant pas dépassé 37 semaines;
4. une **ouverture de l'orifice de l'utérus ne dépassant pas 3 cm;**
5. un **col de l'utérus raccourci de moins de la moitié.**

Les **facteurs de contre-indication clinique relative** sont: la rupture prématurée des membranes, des températures supérieures à 38°C avec suspicion d'infection intra-utérine, des fortes hémorragies par placenta praevia, le détachement prématuré du placenta ainsi qu'une disproportion, par ex. en cas d'étroitesse du bassin.
Les **facteurs de contre-indication médicale relative chez le foetus** sont: l'échantillon de fréquence cardiaque pathologique en l'absence des douleurs du travail, une malformation prouvée, une érythroblastose et une polyhydramnie avec suspicion de malformation.
Les **facteurs de contre-indication médicale relative chez la mère** sont: un diabetes mellitus manifeste et difficilement contrôlable, des maladies cardiaques congénitales, des arrhytmies cardiales, l'hyperthyreose et une hypertonie grave. Une administration simultanée de calciumions accroît la tendance de vibrations ventriculaires.

3. Indications pour la tocolyse

1. **Travail prématuré** avec risque d'accouchement prématuré.
2. **Régulation du travail** en cas d'hyperactivité de l' utérus, tetanus uteri,
   antidote en cas de stimulation excessive par oxytocine ou prostaglandines.
3. **Opération** pendant la gravidité,
   cerclage,
   myomenucleation,
   transfusion intrafoetale en cas d'érythroblastose,
   autres opérations abdominales.
4. **Urgences obstétriques,**
   omphaloproptose,
   tropisme et extraction,
   placenta incarcerate,
   involutio uteri post partum.
5. **Hémorragie placentaire** de faible à mésosthénique jusqu'à la 37ème semaine de gestation.
6. **Asphyxie intra-utérine** dans la période d'expulsion.
7. **Gestose.**

4. Le traitement clinique de l'accouchement prématuré

Le traitement clinique de l'accouchement prématuré menaçant peut être appliqué en accord avec les directives suivantes:

a) Repos au lit et sédation légère dans les cas d'activité utérine prématurée et irrégulière.

b) Thérapie tocolytique et spasmolytique combinée dans les cas où l'activité utérine continue devient régulière et plus forte.

Le **traitement intensif** commence par voie intraveineuse avec des β stimulateurs, par ex. Th 1165a 1—3 μg/min, pour prévenir les effets secondaires verapamil 120 μg/min dans du glucose à 5%.
Traitement de longue durée par voie buccale Th 1165a 3—5 mg toutes les 4—6 heures, avec, en plus, verapamil 40—80 mg toutes les 4—8 heures.
Si ces traitements ne suffisent pas à inhiber le travail, on peut essayer d'administrer 1 g d'aspirine toutes les 6 heures pendant 2 maximum 6 jours par voie buccale ou rectale.

Mots-clés: tocolyse, travail prématuré et son traitment, inhibition du travail, sédatifs utérins, substances β stimulateurs sur l'utérus humain, effet de l'aspirine sur l'utérus humain.

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